

What do we need to  
know about the  
hypertension literature?

## General Knowledge Quiz

Who first described an epidemiological association between high blood pressure and premature death?

- (a) Hippocrates
- (b) Richard Bright
- (c) New York Insurance Company Actuaries in the 1920's
- (d) The Framingham Study Group in 1961

When was the first RCT of hypertension treatment published?

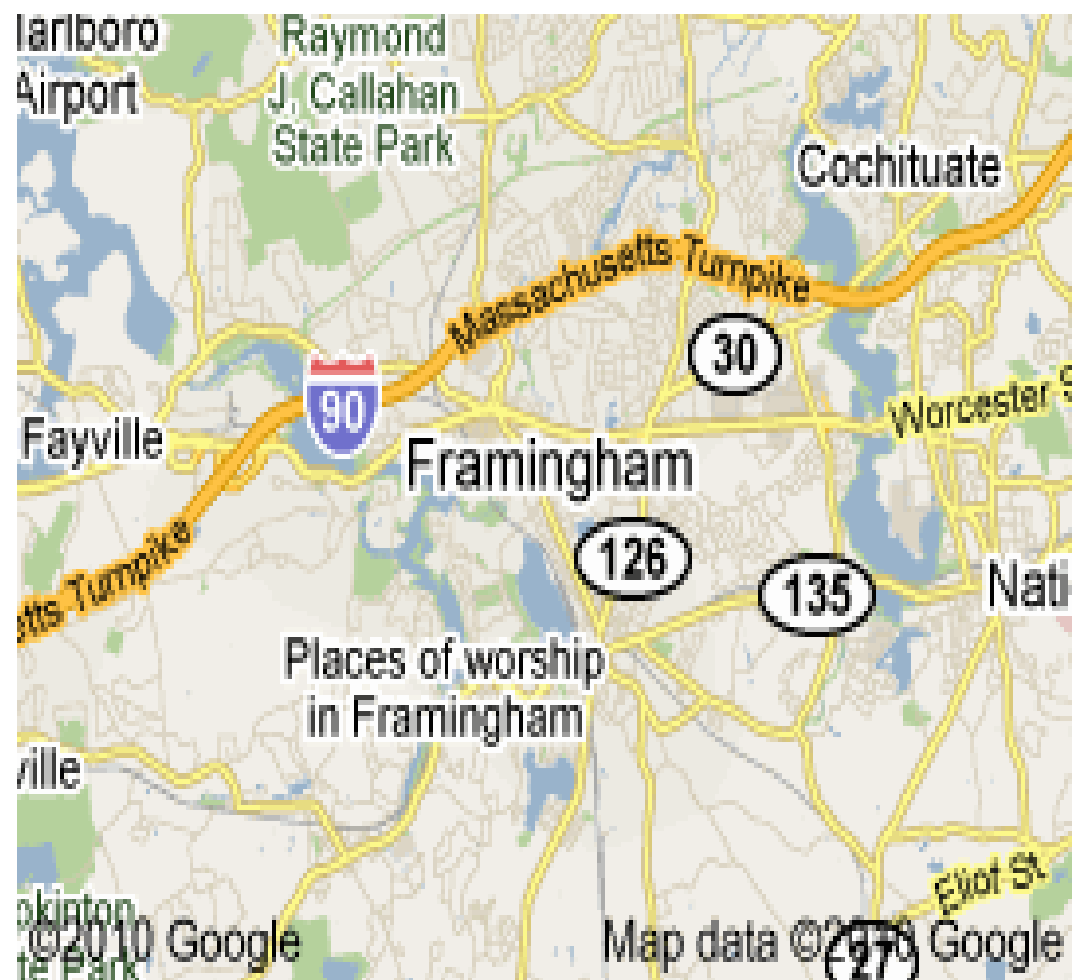
- (a) 1959
- (b) 1967
- (c) 1973
- (d) 1975

What is the largest antihypertensive drug trial ever conducted?

- (a) SHEP
- (b) Syst CHINA
- (c) CAPPP
- (d) ALLHAT

Easy widespread (indirect) blood pressure measurement became possible in the early 20<sup>th</sup> century with the introduction of the mercury sphygmomanometer

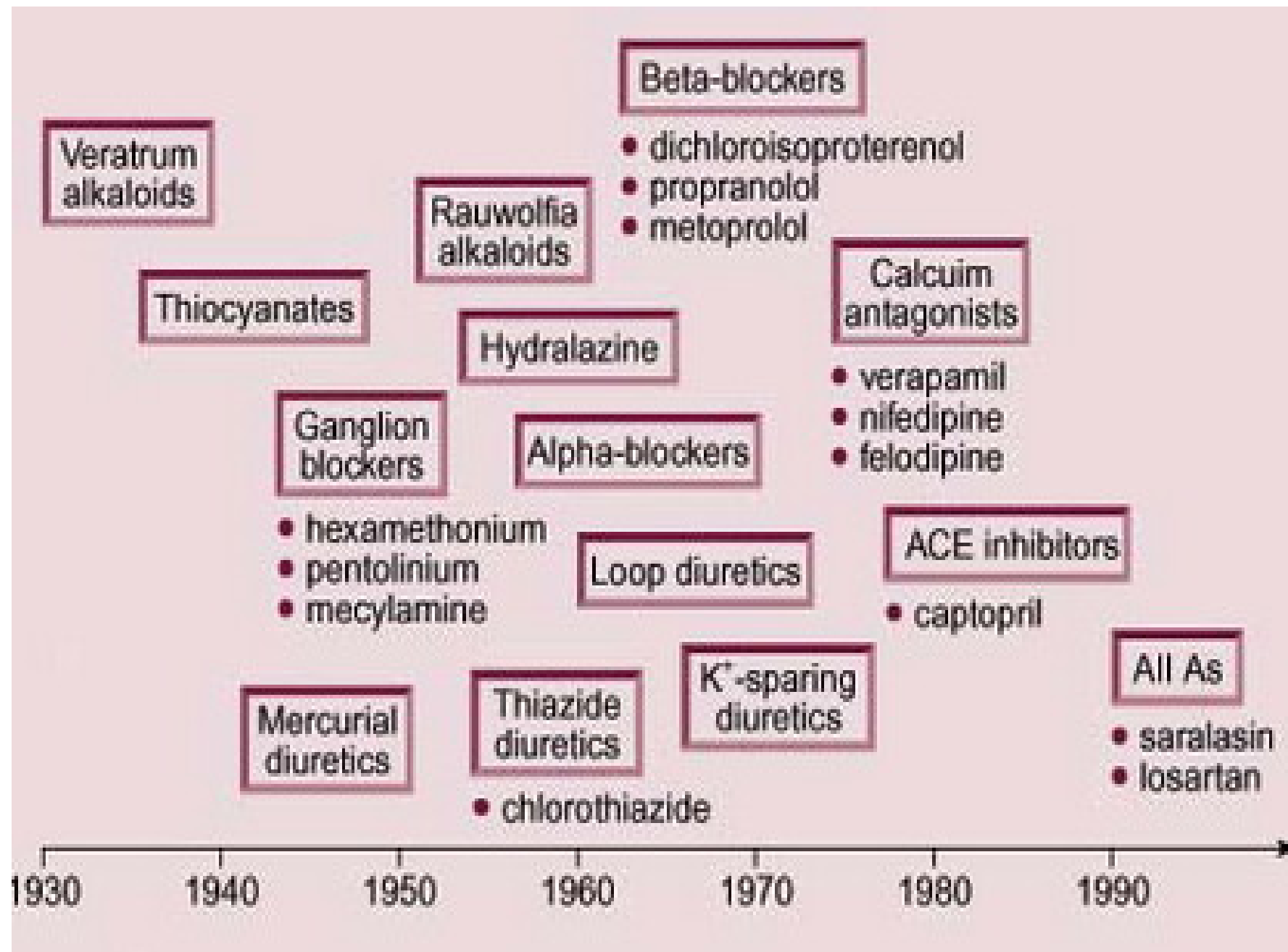
Insurance company actuaries in the 1920's first established clear evidence of association of elevated blood pressure with premature death





Kannel WB et al Ann Intern Med 1961; 55:33

Gradation of increased coronary disease risk with increasing levels of systolic blood pressure and cholesterol



# The VA Cooperative Study, 1967

<b>Cohort</b>	<b>143 men</b>
<b>Mean age</b>	<b>51 years</b>
<b>Eligibility</b>	<b>Diastolic BP 115-129 mmHg</b>
<b>Design</b>	<b>Double blind; placebo control</b>
<b>Therapy</b>	<b>HCTZ, reserpine, hydralazine</b>
<b>Duration</b>	<b>1.5 years</b>
<b>BP change</b>	<b>-43/30 mmHg</b>

HCTZ=hydrochlorothiazide

VA Cooperative Study Group. JAMA. 1967;202:1028-1034.

## Mean follow-up 18 months

	Placebo (70)	Active Treatment (73)
Deaths	4	0
Class A events	10	0
Other treatment failures	7	1
Class B events	6	1
Total events	27 (39%)	2 (3%)



# The VA Cooperative Study, 1970

<b>Cohort</b>	<b>380 men</b>
<b>Mean age</b>	<b>50 years</b>
<b>Eligibility</b>	<b>Diastolic BP 90-114 mmHg</b>
<b>Design</b>	<b>Double blind; placebo control</b>
<b>Therapy</b>	<b>HCTZ, reserpine, hydralazine</b>
<b>Duration</b>	<b>5.5 years (mean=3.8 yrs)</b>
<b>BP change</b>	<b>Diastolic BP -19 mmHg</b>

Mean follow-up 3.8 years

	Placebo (194)	Active Treatment (186)
Deaths	19	8
Class A events	9	0
Other treatment failures	7	1
Class B events	21	13
Total events	56 (28.9%)	22 (11.8%)

## 2 types of antihypertensive treatment studies

<b>Efficacy Studies</b>	<b>Outcome Studies</b>
<p data-bbox="275 507 1032 555">Do the drugs lower blood pressure?</p> <p data-bbox="275 740 1043 1011">Most show that all classes of antihypertensives are approximately equally effective although efficacy of particular class may vary by age and race</p>	<p data-bbox="1135 507 1839 667">What is the long term outcome in treated patients? (survival and cardiovascular events)</p> <p data-bbox="1135 740 1957 1129">The bulk of the evidence points to blood pressure lowering being the main determinant of outcome, although this remains contentious, and some recent studies point to a possible antihypertensive class effect on outcome</p>

# 1970's – 2000

- Many larger randomised outcome trials looking at milder forms of hypertension
- New drugs coming on stream to challenge primacy of thiazides and beta blockers
  - ACE-inhibitors
  - Calcium channel blockers
  - Alpha blockers

# The MRC Trials

- **MRC Trial of Mild Hypertension. BMJ 1985;281:97**
  - Middle aged subjects with mild-moderate hypertension (DBP 90-109): thiazide vs propranolol vs placebo.
  - Cardiovascular events reduced in treated groups
  - No difference between propranolol and placebo
  - Benefit for stroke >more than coronary events
- 
- **MRC Trial of Treatment of Hypertension in Older Adults. BMJ 1992;304:405-412**
  - Atenolol vs HCTZ/amiloride vs placebo in pts aged 65-74 with mean SBP160-209mmHg and mean DBP < 115mmHg
  - 4396 pts followed for 5.8 years
  - Results
  - HCTZ/amiloride reduced risk of stroke, coronary events and all cardiovascular events cf placebo. Beta blocker treatment had no significant benefit on either endpoint

**SHEP** (JAMA 1991, 265:2355)

ISH (SBP > 160) in pts > 60 yrs. Designed to look at effect on fatal + non-fatal stroke outcome. Chlorthalidone +/- atenolol vs placebo. Mean f/u 4.5 yrs. Active grp 143/68. placebo 155/72. Stroke incidence in active grp dec by 36%. Non-fatal MI + coronary death also reduced

**UKPDS** (BMJ 1998;317:713)

Atenolol equivalent to captopril in BP lowering and protection against microvascular disease in pts not selected as at increased risk for CV disease

**CAPP** (Lancet 1999, 353:611)

**NORDIL** (Lancet 2000; 356:359)

**STOP 2** (Lancet 1999; 354:1751)

**INSIGHT** (Lancet 2000; 356:359)

**SYST EUR**

**SYST CHINA**

..and a number of other large RCT's suggested BP-lowering as main cause of improved CV outcomes (rather than antihypertensive class). Most evidence fro stroke prevention in older individuals for thiazides and CCB's

## Important studies suggesting outcome benefit for antihypertensive class

**HOPE** (Circulation 2001; 104:522-6) Ramipril vs placebo (got equiv BP lowering with non-ACE/ ARB regimen) in high risk hypertensive > 55yrs. Reduced CV morbidity + mortality for Ramipril-based group

**LIFE** (Lancet 2002; 359:995-1002) 9191 hypertensives aged 55-80 with LVH on ECG randomised to losartan or atenolol-based regimens. Equiv. BP lowering. Significantly worse stroke and CHD outcomes in atenolol-based group

**AASK** African Americans with hypertension and CKD. Slower progression with ramipril vs amlodipine-based regimens

**IDNT** Hypertension with DM2 and proteinuria – improved renal outcomes with Irbesartan (ARB) vs Amlodipine-based regimen

**RENAAL** Hypertension with DM2 and proteinuria – improved renal outcomes with Irbesartan (ARB) vs conventional (non-ACE/ARB) treatment

# ALLHAT Trial (**A**ntihypertensive and **L**ipid- **L**owering **T**reatment to prevent **H**eart **A**ttack **T**rial — *Hypertension* 2003;42:239)

Randomised prospective study involving ~ 45 000 pts, 55yrs + with hypertension and at least 1 other additional risk factor for CAD or diabetes.

Randomised to receive chlorthalidone, doxazosin, amlodipine, or lisinopril as primary drug

|

2nd line drugs reserpine, clonidine, atenolol (most got atenolol)

|

3rd line drug - hydralazine



Primary outcome - combined fatal CAD and non-fatal MI

Secondary outcomes - All cause mortality

Stroke

Combined cardiovascular events including  
CHF

Exclusion Criteria      EF < 35% or symptomatic heart failure

Doxazosin arm discontinued in 2000 - excess of heart failure events cf chlorthalidone arm (**Doxazosin 8.1% risk of HF cf 4.5% for chlorthalidone RR 2.04**)

Results - mean follow-up 4.9 years

Mean BP 146/80 - 135/75 (end of study)

Lisinopril arm had 2mmhg higher SBP and Amlodipine arm 1mmHg higher SBP than the chlorthalidone arm

### Primary outcome

Identical for chlorthalidone lisinopril and amlodipine groups (6 year rate 11%)

### Secondary outcomes

*All cause mortality* - identical in the 3 groups

Lisinopril vs chlorthalidone group - more combined CV disease (33.3 vs 30.9%), stroke (6.3 vs 5.6%) and heart failure (8.7 vs 7.7%) (RR 1.19)

**Amlodipine vs chlorthalidone group – more heart failure (10.2 vs 7.7%, RR 1.38)**

Heart failure risk for lisinopril vs chlorthalidine disappeared after 1st year but amlodipine vs chlorthalidine persisted throughout the study

SBP difference at the end of the study can't explain all the difference in outcome

NB Most of the difference in heart failure in Lis. Vs Chlor would be abolished by removing the African-American group who had end of study 4mmHg higher SBP than Chlor. Group.

### Interpretation of the Trial Results

**Thiazide-type diuretics are at least as good as other antihypertensives in preventing mortality and adverse cardiovascular outcomes and are cheaper, so should remain the drugs of first choice.**

For heart failure prevention thiazides are better than CCB (and ACE-I in the 1st year).

Modest BP difference does not explain the total effect

JNC 7 Guidelines (JAMA 2003;289:2560-2572))

Classification of Blood Pressure

<u>Category</u>	<u>SBP</u>		<u>DBP</u>
Normal	< 120	or	< 80
Prehypertension	120-139	or	80-89
Stage 1	140-159	or	90-99
Stage 2	> 160	or	> 100

## JNC-7 Blood Pressure Treatment

Treat to BP < 140/90 or < 130/80 with diabetes or CKD

Start with lifestyle modifications

### Without compelling indications

#### Stage 1

Thiazide for most

#### Stage 2

Thiazide + ACE-I, ARB, BB, or CCB

### With compelling indications

Drug(s) for compelling indications

### Not at goal BP

Optimise dosages or add drugs until goal BP achieved

Most people will require at least 2 drugs

**Renal Outcomes in High-Risk Hypertensive patients treated with an ACE-inhibitor or calcium channel blocker vs a diuretic – a report from the ALLHAT Trial. Rahman M et al. Arch.Intern.Med 2005;165:936-946)**

Renal outcome was not a major focus of ALLHAT and baseline creatinine > 200mg/dl (177umol/l) was exclusion to enrolment.

1049 participants progressed to ESRF (2%)

No significant difference in incidence of ESRF or composite renal outcomes in chlorthalidone vs amlodipine and lisinopril groups

Results comparable for diabetics and non-diabetics

Chief deficiency No proteinuria data collected

**Cardiovascular outcomes in High-Risk Hypertensive patients stratified by baseline GFR. Rahman M et al. Ann.Intern.Med.2006;144(5):172-180**

Same investigators as above paper using ALLHAT data looking at cardiovascular outcomes stratified by baseline GFR. Stratified into 3 GFR groups:- > 90ml/min (mean 102.5) , 60-89 (Mean 75.1) ml/min and < 60ml/min (mean 50.6). Baseline characteristics of the C, A and L arms were similar in each of the 3 groups.

6 year event rates

All

	ESRD	CHD	Combined CVD
High GFR	0.4%	8.5%	26.5%
Middle GFR	1%	10.8%	30.5%
Low GFR	6%	15.4%	40%

Diabetes at baseline

	ESRD	CHD	Combined CVD
High GFR	0.5%	9.7%	29.6%
Middle GFR	2%	13.9%	40%
Low GFR	10.8%	19.6%	45.5%

## Outcome by Drug

Neither amlodipine nor lisinopril is superior to chlorthalidone in preventing fatal CHD and non-fatal MI in pts with hypertension who have reduced GFR. Neither amlodipine nor lisinopril is superior to chlorthalidone in preventing CHD, stroke or combined CVD, and chlorthalidone is superior to both for preventing heart failure independent of baseline renal renal function

## Summary

Older individuals with hypertension and reduced GFR are at far greater risk of cardiovascular events (and death) than development of ESRD



## Was there any down side to thiazide diuretic in ALLHAT?

### **New onset diabetes after 4 years**

- chlorthalidone 11%
- amlodipine 9.3%
- lisinopril 7.8%

There is evidence that new onset diabetes does increase the risk of CV events although it is still disputed whether drug-induced diabetes carries the same risk (*Verdecchia. Hypertension 2007;50:459-460*).

There is also some evidence that thiazide-induced DM can be avoided by rigorous correction of hypokalaemia. (*Bloch MJ Basile. Correction of thiazide-induced hypokalemia prevents hyperglycemia and incident diabetes mellitus J.Hypertension 2006;48:219-24*)

## Can ACE-inhibitors prevent diabetes?

DREAM Trial (*Diabetes REduction Assessment with ramipril and rosiglitazone Medication. Lancet 2006;368:1096-1105*)

2x2 factorial design in which both ramipril and rosiglitazone (separately) compared with placebo in pts with impaired fasting glucose or impaired glucose tolerance. 5269 randomised to rosiglitazone or placebo and 5808 to ramipril or placebo. Followed for 3yrs. Primary outcomes NOD or death, secondary outcomes were fasting glucose levels, regression to normoglycaemia and composite of cardiorenal events.

### Results

New onset diabetes not significantly reduced with ramipril (18.1% vs 19.5% in placebo grp) even when correcting for other medications (thiazides and beta blockers) known to affect glucose tolerance. (Ramipril did significantly increase regression to normoglycaemia).

(Rosiglitazone did significant reduce incidence of NOD, but whether this is a true prevention effect or simply a treatment effect will be determined after pts retested after a washout period).

**ASCOT** (The Anglo-Scandinavian Cardiac Outcomes Trial.  
*Lancet 2005;366:895*)

RCT of 19342 hypertensive pts with at least 3 risk factors for CAD assigned to receive amlodipine (+/- perindopril) or atenolol (+/- HCTZ). Mean baseline BP 164/95 and target 140/90 (130/80 in diabetics)

Combined Primary outcomes fatal coronary events + non-fatal MI

Secondary outcomes all-cause mortality, stroke, all coronary events, total cardiovascular events and procedures and non-fatal and fatal heart failure

Results Trial prematurely stopped after a median 5.5 yrs to worse outcomes in atenolol-treated group.

Amlodipine group had lower risk of:

- Primary endpoint (fatal + non-fatal MI) (8.2 vs 9.1/ 1000 pt yrs RR 0.9)
- Fatal + non-fatal strokes (6.2 vs 8.1/ 1000 pt yrs RR 0.77)
- Total cardiovascular events + procedures (27.4 vs 32.8/ 1000 pt yrs RR 0.84)
- All cause mortality (13.9 vs 15.5/ 1000 pt yrs RR 0.89)
- Developing diabetes (11 vs 15.9/1000 pt yrs RR 0.7)

There was a slight BP advantage for the amlodipine group (3/2) but this would not account for  $> \frac{1}{2}$  the outcome benefit

## ASCOT Spironolactone Substudy

(Chapman et al Hypertension 2007;49(4):839-845)

In ASCOT study in order to achieve BP targets Doxazosin 4-8mg was 3<sup>rd</sup> drug add-on; if BP still uncontrolled 4<sup>th</sup> drug left to investigator's discretion but moxonidine or spironolactone suggested. 1790 received SPTN, but 212 for non-BP reasons and 167 insuff. data so 1411 available for analysis.

Mean dose 25mg; mean BP starting SPTN (on ave 2.9 other drugs) 156.9/85.3

Mean BP fall 18/11.5 (to 135.1/75.8) / effect independent of gender, diabetic status, or concomitant use of thiazides or ACE-inhibitor.

Gynaecomastia or breast discomfort – 6% of men (leading to discontinuation in ½)

4% serum K > 5.5mmol/l 2% > 6mmol/l

1% serum Na < 130

Cessation of SPTN due to biochem abnormalities – 2%

Largest and best study to date evaluating SPTN use in resistant hypertension / 2006 BHS guidelines suggest SPTN as 4<sup>th</sup> drug in RH.

## CAFÉ Substudy of ASCOT (*Conduit artery function evaluation*)

Circulation 2006;113(9):1213-25

2199 participants were enrolled in a substudy where they had measurements of radial applanation tonometry + pulse wave analysis – used to derive central aortic pressures + haemodynamic indexes at repeated visits over 4 years.

Result Amlodipine pts had significantly lower central aortic pressures (~4mmHg) than atenolol despite similar brachial blood pressures.

Conclusion Better CV outcomes in amlodipine cf atenolol grp may be due to differential effects on central aortic pressures rather than a specific benefit of the particular drugs/ central aortic BP is the BP the vital organs are actually exposed to.

Measurement of central aortic BP may become more important in clinical practice.

**SphygmoCor** device available (manufactured in Australia) but currently costs > \$20 000.

## **Are Beta Blockers Appropriate as Initial Therapy in Hypertension?**

Beta blockers are effective anti-anginals and are clearly indicated post-MI where there is strong clinical trial evidence for their use in preventing reinfarction. It is unclear however whether in the absence of these indications they offer much cardioprotective effect. Cardioprotection by beta blockers was suggested by some early studies, but this has not been borne out in later studies, some even suggesting worse outcomes on beta blockers (including ASCOT).

### **Meta-analysis Lancet 2005;366:895**

13 RCT's, 106 000 pts – adverse outcomes associated with atenolol but not other beta blockers. All beta blockers are associated with an increased risk of stroke, but non-atenolol beta blockers (alone or in combination with diuretics) are not associated with increased risk of MI or all-cause death

### **Meta-analysis CMAJ 2006;174:1237-42**

Benefits for younger patients, but not the elderly from beta blockers

**Drug-induced diabetes** – the diabetogenic potential of thiazides is significantly magnified by coexisting beta-blocker use making this combination now quite unattractive. Given that thiazides are currently “indispensable” – further reason to avoid beta blockers.

## 2006 BHS/NICE Guidelines

Modified classification of blood pressure

(A= ACE-I or ARB, C = CCB, D = thiazide diuretic)

< 55yrs

A

> 55yrs

Cor D

Step 1



A+ C   or   A+D

Step 2



A+C+D

Step 3



Add further diuretic

Step 4

or Alpha blocker

or Beta Blocker

Consider seeking specialist advice



2007 ESH/ESC Guideline

J.Hypertens.2007;25(6):1105-1187

Modified classification of blood pressure

Complex difficult to summarise guideline

Beta blockers not excluded – start treatment with one of five groups of drugs

Thiazide

ACE-Inhibitor

ARB

Beta Blocker

CCB

American Heart Association Guideline (*Treatment of hypertension in the prevention and management of IHD. Circulation 2007;115(21):2761-2788*)

BP goal < 130/80 for pts with CAD and CAD risk equivalents including:

- carotid artery disease
- peripheral vascular disease
- abdominal aortic aneurysm
- Framingham 10yr risk score > 10%

Pts with CAD and elevated diastolic pressure (concern re J curve)

- reduce DBP slowly
- maintain DBP > 60mmHg

## Prehypertension (130-140 +/- 80-90)

TROPHY Trial (*Feasibility of treating prehypertension with an ARB.*  
*N.Engl.J.Med.2006;354:1685-97*)

800 adults (ave. age 48.5 yrs) with prehypertension randomised to candesartan 16mg daily or placebo and followed for 2 yrs; then candesartan stopped and both grps followed for further 2 yrs.

During 1<sup>st</sup> 2 yrs 53pts in candesartan grp developed hypertension and 154 in placebo grp; after further further 2 years 208 pts in candesartan grp and 240 pts in placebo grp had developed hypertension ( $p<0.07$ )

### Conclusions

- Nearly 2/3 untreated prehypertension progressed to hypertension in 4 years
- Onset of hypertension may be able to be delayed by treatment of prehypertension
- Would intervention at an even earlier stage help ? children and adolescents with high/normal blood pressure
- Trialists relatively young/ applicability to older age groups uncertain



## Chlorthalidone vs Hydrochlorothiazide

- C. Is not actually a thiazide but a thiazide-like molecule with a distinct pharmacokinetic profile, including a very long elimination T<sub>1/2</sub> -22-55hrs cf 2.5 hrs for HCTZ
- 12.5mg C. ~ dose equivalent to 25mg HCTZ, but better 24 hour BP profile on ABPM  
(*Comparative antihypertensive effects of HCTZ and chlorthalidone on ambulatory and office BP. Ernst et al. Hypertension 2006;47:552-8*)
- C. works down to lower GFR than HCTZ
  - HCTZ ineffective below 30-40ml/min
  - C. effective down to 20-30ml/min/ therefore a useful drug in CKD
- Most large hypertension clinical trial data showing benefit from thiazides is with chlorthalidone, including early MRC studies and ALLHAT
- Majority of outcome studies of hypertension in elderly populations showing benefit from diuretics have used chlorthalidone
- At Rush Presbyterian Hypertension Clinic single commonest effective manoeuvre in resistant hypertension is replacing HCTZ with chlorthalidone. (*Garg JP, Elliot WJ, Folker A et al. Resistant Hypertension revisited: a comparison of two university-based cohorts. Am J Hypertens. 2005;18:619-626*)

## Ambulatory BP Monitoring

Recommended thresholds (*O'Brien et al. J.Hypertens.2003;21:821-848*)

	<b>Optimal</b>	<b>Normal</b>	<b>Abnormal</b>
<b>Awake</b>	< 130/80	<135/85	>140/90
<b>Asleep</b>	<115/65	<120/70	>125/75

*Ambulatory BP Monitoring (Review) Pickering et al. N.Engl.J.Med 2006;354:2368-2374*

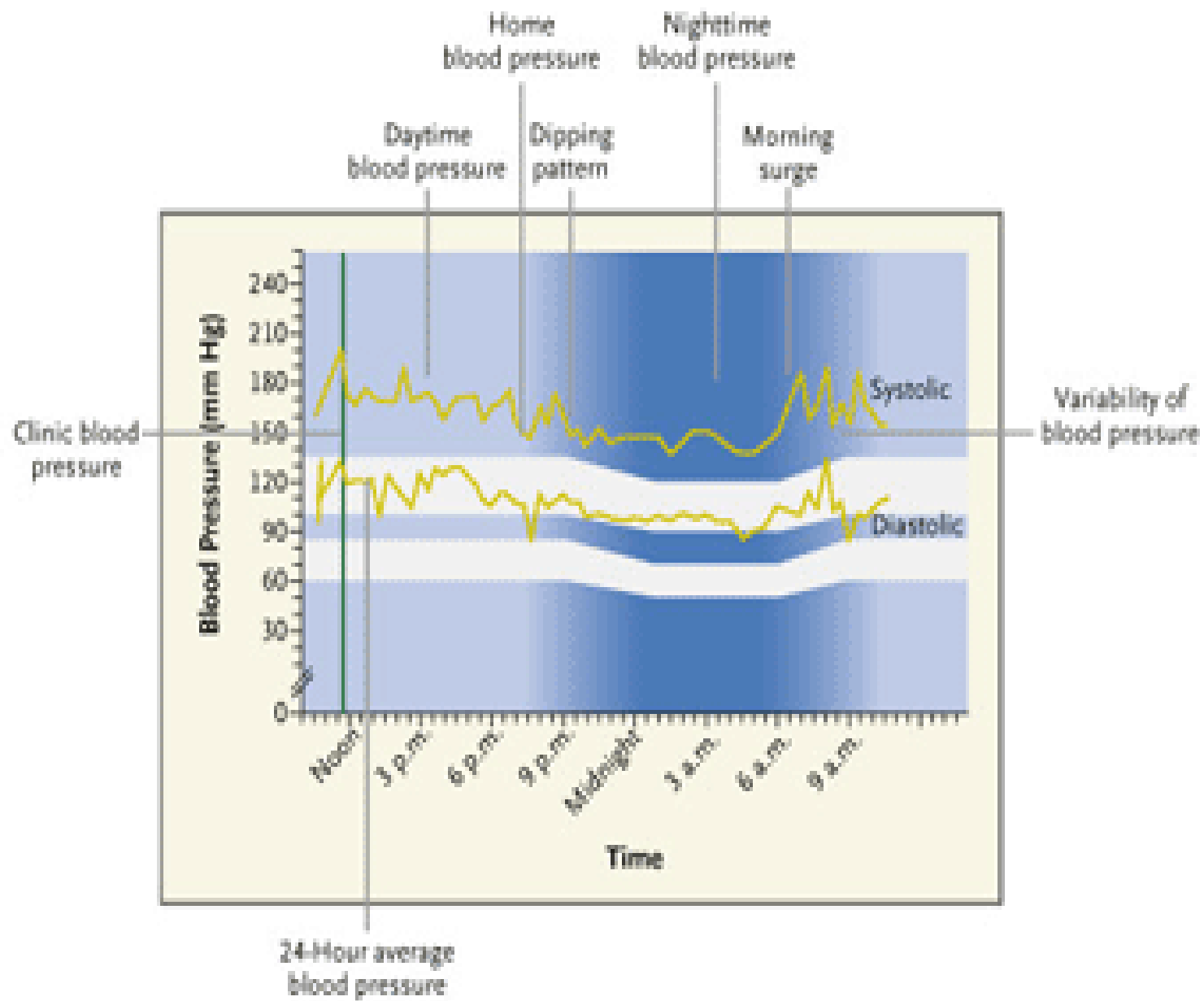
*The role of ambulatory BP monitoring in chronic and end stage renal disease. Kidney Int.2006;70:1000-7*

*Masked Hypertension (Review) Pickering. Hypertens.Res.2007(6) 479-88*

*Morning hypertension: the strongest independent risk factor for stroke in elderly hypertensive patients. Ishikawa et al. Hypertens.Res.2006;8:581-7*



13 9:54





## Advantages of ABPM

- White coat hypertension
- Assessment of Day-Night BP Changes
  - Dippers/ Non-Dippers/ Extreme Dippers/ Masked Hypertension/ Morning Hypertension
- Better correlation with target organ damage
- Non-dipping an important CV risk factor – common in states of sympathetic overactivity eg diabetes and CKD/ESRD
- Allows tailoring of medical therapy:
  - eg night-time dosing to improve nocturnal dipping or suppress morning surge of BP (one of the possible explanations of the worse outcome in the Atenolol group in ASCOT study was morning BP surge due to once rather than twice daily atenolol dosing).
- Majority of recent and current hypertension trials use ABPM in addition to or instead of office BP recordings

## Hypertension in the Elderly

Different disease – due to aortic stiffness rather than increased peripheral resistance. Almost exclusively systolic hypertension (DBP falls after ~ 55yrs)

Efficacy and outcome studies (MRC, SHEP, STOP, HDFP, Syst-Eur) up to 80 yrs of age show benefit of BP lowering and that thiazides and long acting CCB's are most effective as single agents (monotherapy with Beta blockers, ACE-inhibitors and ARB's often ineffective in this age group, but ACE-inhibitor/diuretic combination is effective)

### Thiazide or CCB?

Both reduce CAD and stroke equivalently, but CCB less effective at preventing CHF (which is commonest cause of hospitalisation in elderly), so thiazides probably preferred.

### What about the very old?

HYVET (*HYpertension in the Very Elderly Trial*) placebo controlled trial of low dose indapamide (+/-perindopril if required) for systolic, diastolic and isolated systolic hypertension in pts > 80yrs. Preliminary results in 3845 pts show significant reduction in stroke and mortality in treated group.

### What about the J-shaped curve?

SHEP. (*JAMA* 1991;265:2355) and INVEST (*JAMA* 2003;298:2859-61) both showed worse cardiovascular outcomes in elderly pts with very low diastolic BP.

Post-hoc analysis of Syst-Eur (*Arch Intern Med* 2007;167:1884-1891) concluded no excess risk in ISH pts where DBP > 55mmHg.

A clinical trial is needed comparing active Rx with placebo in elderly pts with baseline SBP 140-160 and DBP < 70.

In the meantime, the consensus is that “in the majority of older patients with ISH, antihypertensive therapy should be intensified until SBP reaches < 140mmHg or < 130 in pts with DM or CKD, at least until the DBP reaches 55mmHg. For individuals with underlying CHD, antihypertensive therapy should be intensified with caution in pts whose DBP is lowered to < 70mmHg”.

ACE inhibitor + Thiazide

vs

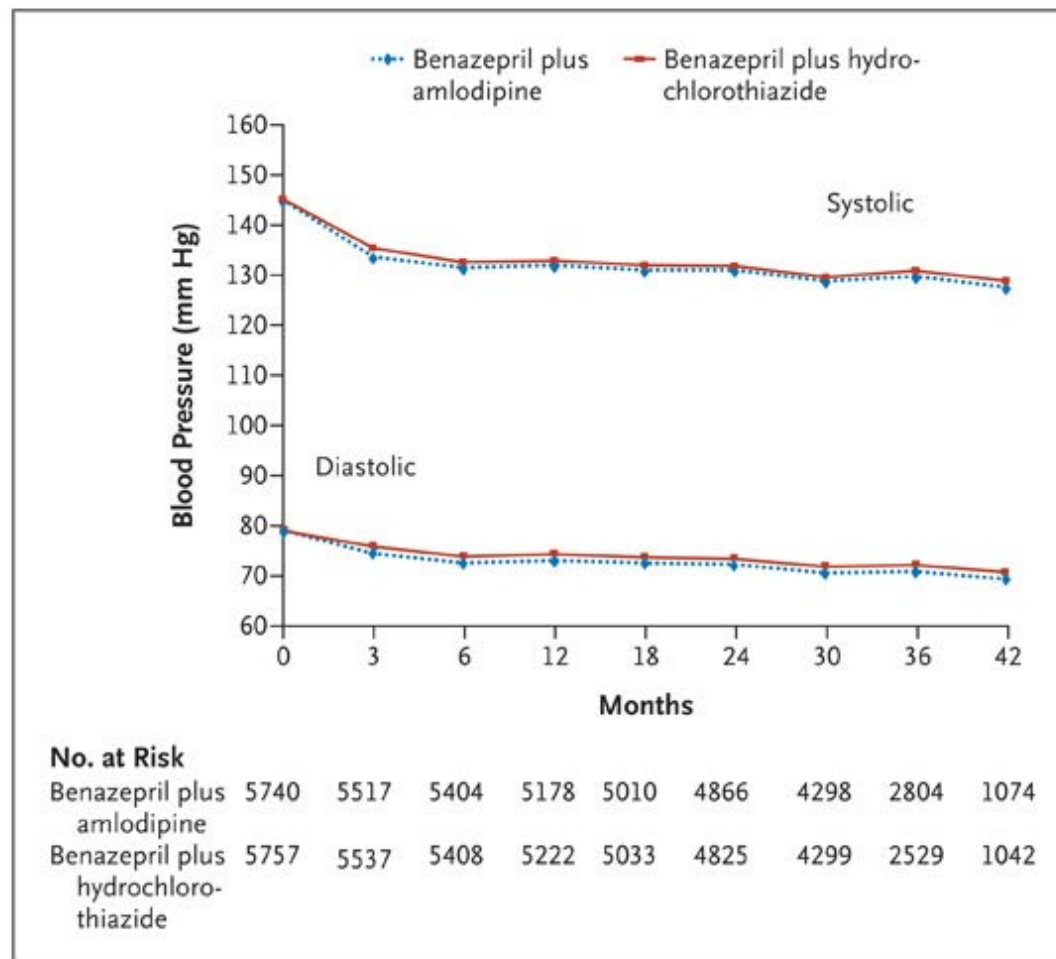
ACE inhibitor + CCB

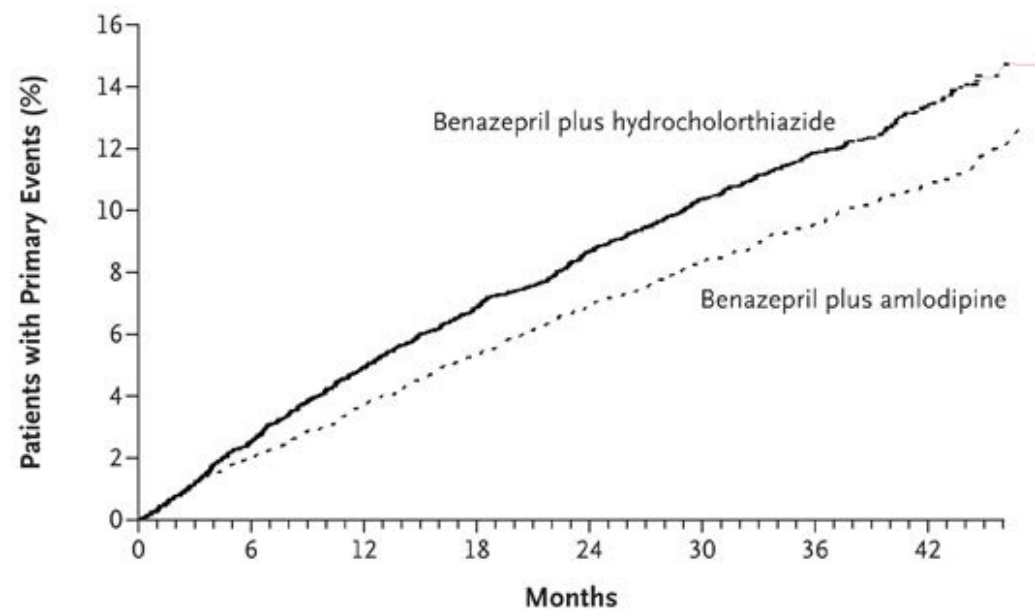
**ACCOMPLISH** (*NEJM* 2008;359:2417-2428) was a large (11 400) outcome study of high risk hypertensives > 55 yrs and SBP > 160 . Many obese and 60% diabetic. Pts randomised to Benazepril/HCTZ or Benazepril/Amlodipine combinations.

Primary endpoint – composite of death from cardiovascular causes, nonfatal MI, nonfatal stroke, hospitalisation for angina, resuscitation after cardiac arrest, and coronary revascularisation

Pts randomised from 2003.

Excellent BP control with 76% having BP at target at 18 months and few dropouts for side effects. 50% obese 60% diabetes mellitus



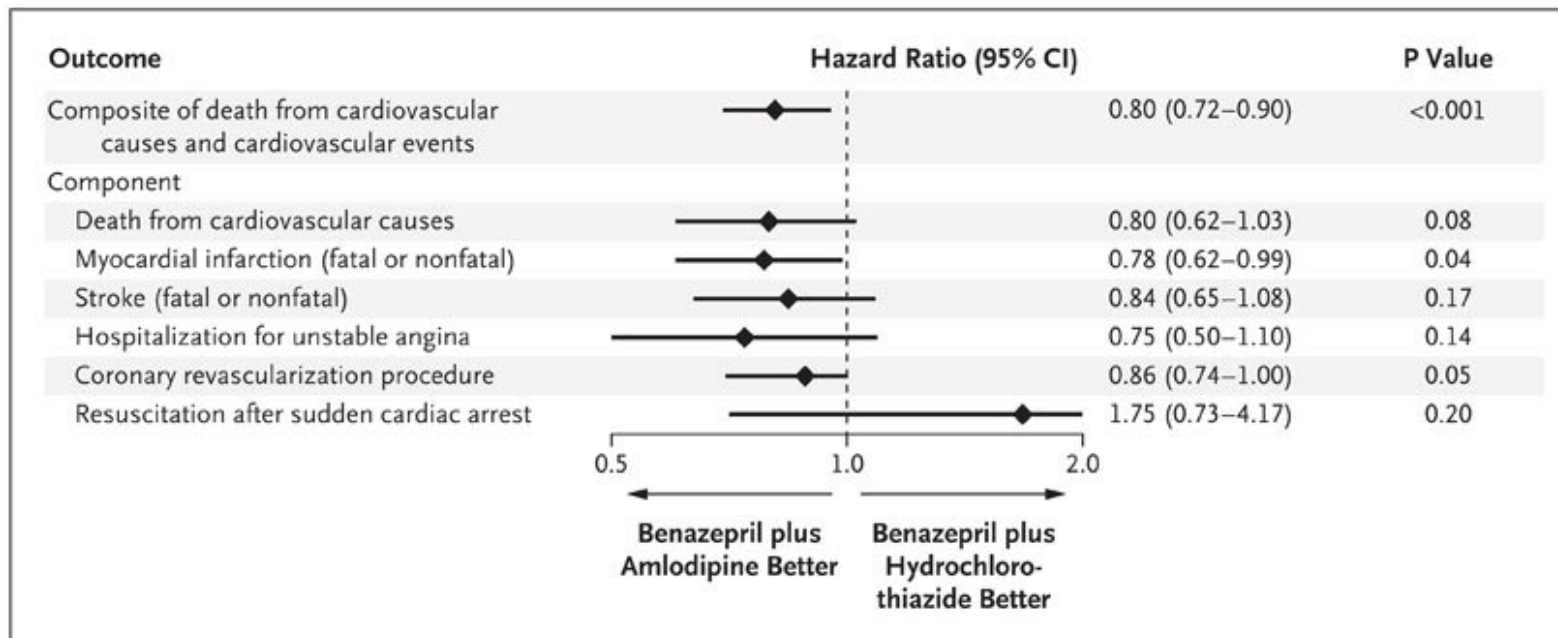


**No. at Risk**

Benazepril plus amlodipine	5512	5317	5141	4959	4739	2826	1447
Benazepril plus hydrochlorothiazide	5483	5274	5082	4892	4655	2749	1390



The NEW ENGLAND  
JOURNAL of MEDICINE





Trial stopped early in October 2007 by data safety and monitoring committee following interim analysis of 60% of expected information from the trial.

Over a mean f/u of 39 months, cardiovascular morbidity/mortality was reduced by 20% with the ACEI/CCB compared with the ACEI/HCTZ

**“The benazepril-amlodipine combination was superior to the benazepril hydrochlorothiazide combination in reducing cardiovascular events in patients with hypertension who were at high risk for such events”**

# Treatment of Hypertension in Patients 80 years of Age or Older (HYVET Study)

N.Engl.J.Med.2008;358:1887-98

- In this study, patients 80 years of age or older with sustained systolic hypertension were randomly assigned to receive either the diuretic indapamide, with or without the angiotensin-converting-enzyme inhibitor perindopril, or matching placebos, for a target blood pressure of 150/80 mm Hg

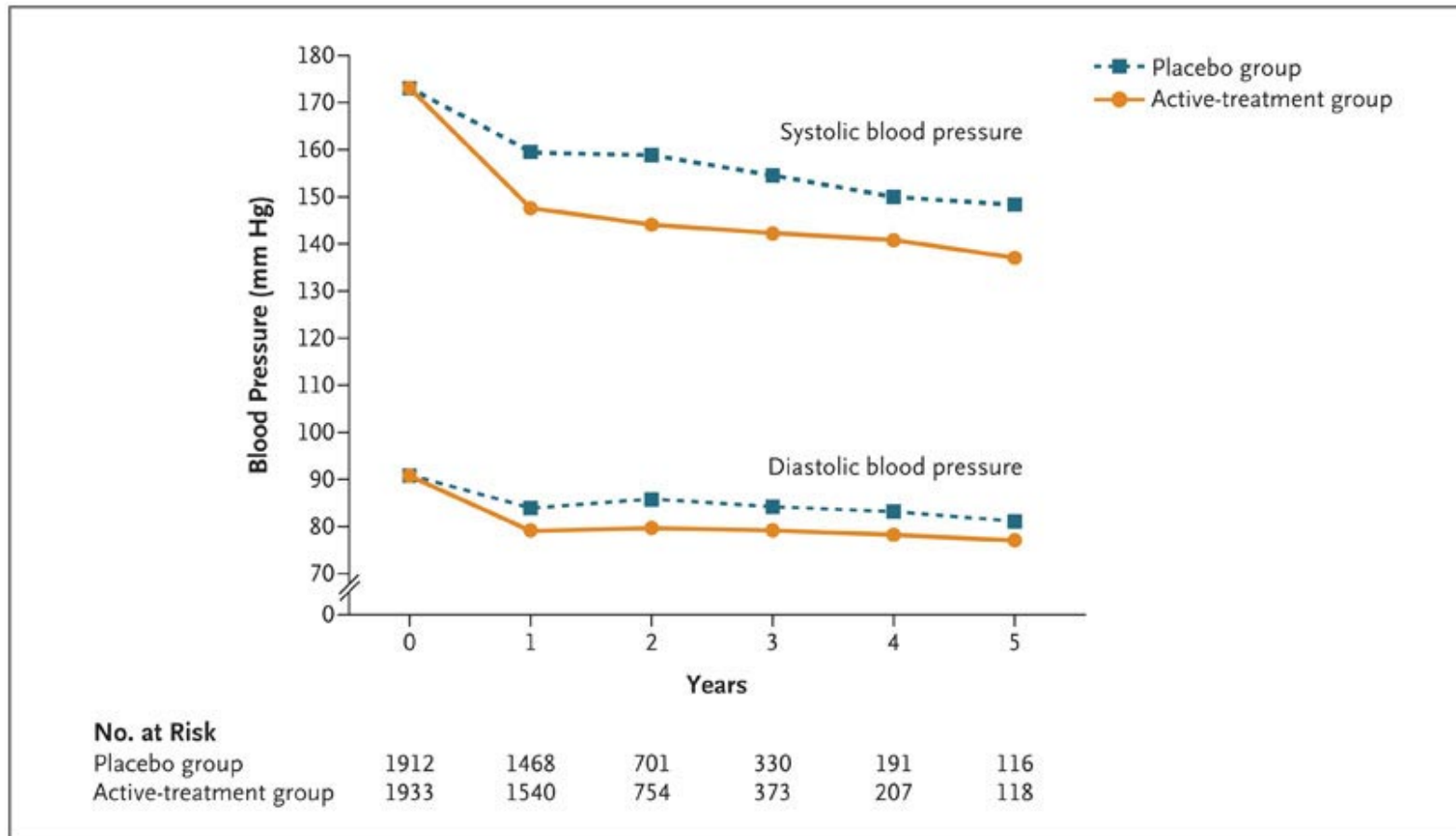
1933 patients on active treatment and 1912 placebo

Mean age 83.6 years (both groups)

Mean seated BP 173/90 (both groups)

Mean BP reduction in treatment group 15/6.1

Followed for mean 4 years



Treatment Group had:

- 30% reduction in in rate of fatal or non-fatal stroke
- 39% reduction in rate of death from stroke
- 21% reduction in rate of death from any cause
- 23% reduction in rate of death from cardiovascular causes
- 64% reduction in rate of heart failure

## THE ACCORD TRIALS

Type 2 diabetics at high risk for cardiovascular disease

**Intensive vs ave glycaemic control** (HbA1C < 6% vs 7%) Mean f/u 3.5 years  
*Worse CV outcomes in intensive glycaemic control group (NEJM 2008, 258:2545)*

**Statin + fibrate vs statin alone** Mean f/u 4.7 years  
No benefit for combination therapy (*NEJM 2010, 362:1563*)

**ACCORD BP Trial** (*NEJM 2010, 362:1575*)

DM2 with A1C > 7.5%

Inclusion Criteria:

SBP 130-180 on  $\leq 3$  meds +  $< 1\text{g}/24\text{ hr}$  proteinuria

Age  $\geq 40$  + CVD or  $\geq 55$  +  $\geq 1$

- anatomical evidence atherosclerosis
- albuminuria
- LVH
- 2 CV RF's (HTN, lipids, smoking, obesity)

Exclusions:

BMI > 45

Creatinine > 1.5mg/dl

Serious illness

Age > 79



Intensive Rx – goals SBP < 120

Standard Rx – goal SBP < 140

### Primary Outcome

composite of non-fatal MI, non-fatal stroke + CV death

### Secondary Outcomes

MACE + revasc or HF hospitalisation

ACS

Non-fatal MI

Non-fatal stroke

Fatal/non-fatal stroke

All-cause mortality

CV death

HF hospitalisation or death

Mean SBP achieved 119.3 vs 133.5

Mean f/u 4.7 years

### Results

No difference in primary outcome between the 2 groups

Stroke rate (a 2<sup>o</sup> outcome) lower (0.32% vs 0.53 pa – p= 0.01) in intensive group

### Conclusion

**In patients with DM2 at high risk for cardiovascular events, targeting a SBP of < 120 cf < 140 did not reduce the rate of a composite outcome of fatal and non-fatal major cardiovascular events**